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RAPID COMMUNICATION

Regression of left ventricular hypertrophy in hypertensive dialyzed uremic patients on long-term antihypertensive therapy

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Regression of left ventricular hypertrophy in hypertensive dialyzed uremic patients on long-term antihypertensive therapy. There have been no studies of the possibility of reversing the left ventricular hypertrophy (LVH) of chronically hemodialyzed hypertensive uremics (HDH) with long-term antihypertensive therapy. We have measured left ventricular sizes of eight (6 male, 2 female, aged 29 to 61 years) HDH with M-mode echocardiography, before and 12, 18 and 24 months after the start of a combined antihypertensive therapy which included ACE-inhibitors, beta-blockers and calcium-antagonists. Pre-treatment values for mean blood pressure (MBP), 116.6 ± 2.9 mm Hg, end diastolic diameter (EDD), 62.6 ± 6.6 mm, interventricular septum (IVS), 14.2 ± 3.0 mm, and left ventricular mass index (LVMi) , 239 ± 61 g/m^2, were all significantly higher than those for nine sex- and age-matched hemodialyzed normotensive subjects (HDN) with comparable hemoglobin (Hb) levels. During the antihypertensive treatment, both the systolic and diastolic BP decreased steadily ($P = 0.0001$; $P = 0.0003$; ANOVA) and significantly by the third month ($P < 0.05$; $P < 0.01$), reaching levels comparable to those of the HDN group after 12 months. At this time the LVMi (204 ± 67) and the IVS (13.1 ± 2.7), although both significantly lower than baseline, were still higher than in the HDN group, while the EDD was similar. After 24 months, however, both the IVS (12.3 ± 3.1) and the LVMi (161 ± 65) were no longer different from those of the HDN group. Thus, this study is the first to demonstrate that prolonged antihypertensive therapy with strict blood pressure control is able to considerably reduce the LVH of chronically hemodialyzed uremic patients, indicating the key role of arterial hypertension in inducing pathological growth of the LVM in these subjects.

It is known that left ventricular hypertrophy (LVH) of essential hypertensives can be reversed by effective antihypertensive therapy [1, 2]. Long standing arterial hypertension is also suspected to be a leading cause of LVH in patients with end-stage renal disease [3, 4]. On the other hand, previous studies of such patients did not demonstrate a clear etiopathogenetic role of arterial hypertension, since LVH progressed with time in spite of adequate blood pressure (BP) control [5, 6]. Furthermore, in a more recent study, oral nitrendipine given for 24 weeks had no measurable effect on the heart size of these subjects, although it significantly decreased the pre-dialysis BP [7]. To date no reports of the effects of strict BP control with prolonged antihypertensive therapy on LVH of chronic hypertensive uremic patients are available.

We have studied prospectively a selected group of dialyzed uremic patients, before and during an antihypertensive regimen lasting two years, by echocardiography.

The data presented here indicate that prolonged antihypertensive therapy effectively lowered the BP of these subjects and considerably decreased the left ventricular mass (LVM).

Methods

Subjects

The subjects in this study were recruited from a cohort of nearly 130 patients currently treated at our hemodialysis unit. Patients who had been dialyzed for less than six months were excluded. Other exclusion criteria were: obesity; diabetes; peripheral, cerebral and coronary vascular diseases; past or recent evidence of myocardial infarction; angina pectoris; recurrent congestive heart failure; significant valvular regurgitations; neoplastic diseases, and anemia with hemoglobin (Hb) lower than 8.5 g/dl.

Routine echocardiograms made during the last few months were reviewed and only subjects with echotracings of optimal quality were selected initially. Patients who agreed to participate in the study underwent 24-hour continuous interdialysis ambulatory BP monitoring (CABPM), which was repeated after a period of one month on placebo treatment. Five patients had already been on antihypertensive therapy. For these patients, the antihypertensive medications were gradually tapered off over a week before they started to take the placebo. Patients were arbitrarily defined as "hypertensive" when their systolic and diastolic BP were >150/90 mm Hg in at least 70% of the total readings from both sets of CABPM, and were defined "normotensive" if their BP were <150/90 mm Hg in at least 70% of the total readings.

Patients who were finally selected included eight (6 males, 2 females, aged 29 to 61 years) hemodialyzed hypertensive (HDH) and nine sex- and age-matched hemodialyzed normotensive (HDN) subjects.

All of them were dialyzed with bicarbonate three times a week, with the duration of treatment (3.5 to 4.5 hr) and dialyzer surface (1.3 to 1.8 m^2), prescribed individually according to the urea-kinetic model criteria [8]. The ideal "dry" body weight was assessed on a clinical basis [9], and for dubious cases, by

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Table 1. Values for eight hypertensive hemodialyzed uremic patients (HDH) and for nine sex- and age-matched hemodialyzed normotensive controls (HDN)

	Basal		12 Months		24 Months	
	HDH	HDN	HDH	HDN	HDH	HDN
Body wt *kg*	63.7 ± 11	64.4 ± 12.7	62.6 ± 11	64.2 ± 14	64.6 ± 12.1	64.1 ± 12.4
Δ Body wt %	3.9 ± 0.7	4.1 ± 0.6	4.2 ± 0.9	4.1 ± 0.9	4.4 ± 1.1	4.2 ± 0.9
Kt/V	1.20 ± 0.09	1.18 ± 0.16	1.22 ± 0.1	1.20 ± 0.1	1.18 ± 0.07	1.21 ± 0.09
Hb *g/dl*	10.1 ± 1.3	10.3 ± 1.4	10.6 ± 1.2	10.2 ± 0.8	11.2 ± 0.9[a]	10.7 ± 1.1
iPTH *pg/ml*	242 ± 253	253 ± 296	279 ± 259	323 ± 322	250 ± 300	336 ± 433
ALP*U/liter*	335 ± 317	414 ± 390	386 ± 536	526 ± 605	335 ± 363	506 ± 590
Al *μg/liter*	15.9 ± 14.2	11.8 ± 8.7	19.9 ± 13.8	16.4 ± 8.0	16.1 ± 7.3	14.2 ± 4.8

Abbrevations are: Δ Body wt, percent intradialytic increase in body weight; Hb, concentrations of hemoglobin; iPTH, plasma parathyroid hormone; ALP, alkaline phosphatase; and Al, serum aluminum.

Data are mean ± SD.

[a] Significant difference ($P < 0.05$) with respect to the first measurement

caval echography [10]. The subjects ate a diet with protein content from 1.1 to 1.2 g/day and unrestricted salt intake. They were taking calcium carbonate or acetate tablets and vitamin D supplements and were given recombinant human erythropoietin (rHuEPO) i.v. or subcutaneously at a dosage adequate for maintaining their Hb levels at about 10 g/dl. There were serial determinations of Hb, plasma aluminum, alkaline phosphatase and intact circulating parathyroid hormone (iPTH; normal values in our laboratory from 10 to 65 pg/ml) was determined by radioimmunoassay (RIA Allegro, Nichols Institute, Texas, USA).

BP was monitored throughout the entire study by measuring supine BP with an automated arm-cuff device. The measurements lasted 15 minutes and were taken monthly during a midweek interdialysis day, just before the next hemodialysis and within 20 minutes after the hemodialysis ended. These three sets of measurements were averaged and the resulting BP level was recorded. For day-to-day purposes, the BP was also measured before and after each dialysis session by a mercury sphygmomanometer. At the end of the study, all subjects of both groups were again monitored by CABPM.

The goal of antihypertensive therapy was to obtain supine DBP within 75 to 85 mm Hg and SBP below 140 mm Hg. The HDH patients were started on oral treatment with 25 mg atenolol and 5 mg lisinopril at the end of each dialysis session and with a daily dose of 20 mg of slow-release nifedipine tablets. In an attempt to ensure strict compliance with the therapy, the post-dialysis therapy was given under the surveillance of a nurse and home therapy was checked by a pill count.

The therapy was titrated every month from the average BP measured with the automated arm-cuff device. If the goal had not been achieved, the dosage of each drug was increased, up to maximal dose of 50 mg atenolol, 10 mg lisinopril every 48 hours and 60 mg nifedipine a day.

All echocardiograms were taken on a midweek interdialysis day. Echocardiograms of HDH patients were made within one week before the start of the antihypertensive regimen and 12, 18 and 24 months thereafter. For the HDN group, records were not taken at the 18th month. The echotracings were collected by a two-dimensional guided M-mode echocardiograph, according to widely accepted criteria [11]. All echocardiograms were taken by the same cardiologist (S.M.), coded by a third party (G.C.) and read at random by an experienced observer (R.D.) who was blind to the subject's identity and to the design of the study. The echocardiographic measurements included the end diastolic diameter of the left ventricular chamber (EDD, normal range in our laboratory 41 to 52 mm), the interventricular septum thickness (IVS, n r: 6 to 11 mm) and the thickness of the left ventricular posterior wall (PW, n r: 6 to 10.5 mm). The intraobserver variability for these measurements in repeated studies averaged 6%. The LVM was calculated from these measurements according to the modified Penn-cube formula [12] and indexed per square meter of body surface area (bsa). The cut-off level for defining LVH was ≥120 g/m^2, which is the highest value we found in our laboratory for a group of 32 normal subjects (20 males, 12 females, aged 20 to 56 years, body wt 45 to 90 kg and bsa 1.34 to 2.1 m^2).

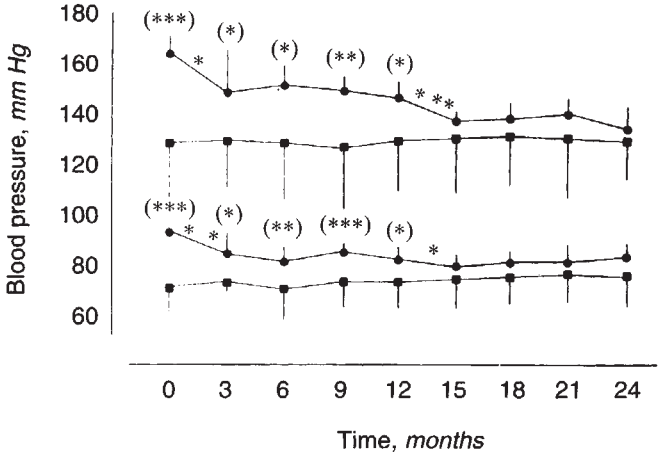

Fig. 1. *Systolic and diastolic blood pressures (mean ± SD) for nine hemodialyzed normotensive uremic patients (■) and for eight hemodialyzed hypertensive subjects (●) on antihypertensive therapy with beta blockers, Ca antagonists and ACE inhibitors for 24 months.* Asterisks indicate significance (***$P < 0.005$; **$P < 0.01$; *$P < 0.05$) with respect to the previous time, or between groups (within parentheses).

Results are presented as means ± SD. Within-patient comparisons were made by analysis of variance for repeated measures (ANOVA). When the F test was significant, then the Student *t*-test was used for comparison of two groups. Differences between patients and control subjects were evaluated by the Student *t*-test for unpaired data.

Table 2. Data for echocardiographically measured left ventricular end-diastolic diameter (EDD), interventricular septum (IVS) and left ventricular posterior wall (PW) for eight hemodialyzed hypertensive subjects (HDH) undergoing antihypertensive therapy with beta blockers, Ca antagonists and ACE inhibitors for 24 months compared to those of nine normotensive sex- and age-matched hemodialyzed uremic subjects (HDN)

	Basal		12 Months		24 Months	
	HDH	HDN	HDH	HDN	HDH	HDN
EDD *mm*	62.6 ± 6.6[e]	54.9 ± 4.7	55.7 ± 7.2[a]	52.6 ± 3.5[c]	49.6 ± 8.2[a]	51.9 ± 3.3[c]
IVS *mm*	14.2 ± 3.0[d]	9.9 ± 1.4	13.1 ± 2.7[c,d]	9.2 ± 1.2	12.3 ± 3.1[c]	10.0 ± 1.4
PW *mm*	10.4 ± 1.4[f]	8.9 ± 0.9	11.4 ± 1.9[c,e]	9.4 ± 0.8[c]	11.0 ± 2.3	10.1 ± 1.1[b]
IVS/PW	1.36 ± 0.2[f]	1.12 ± 0.2	1.15 ± 0.2[c]	0.99 ± 0.1[c]	1.11 ± 0.1[a,f]	0.99 ± 0.1

[a] $P < 0.01$, [b] $P < 0.02$, [c] $P < 0.05$ indicate differences with respect to the basal values
[d] $P < 0.005$, [e] $P < 0.02$, [f] $P < 0.05$ indicate differences between groups

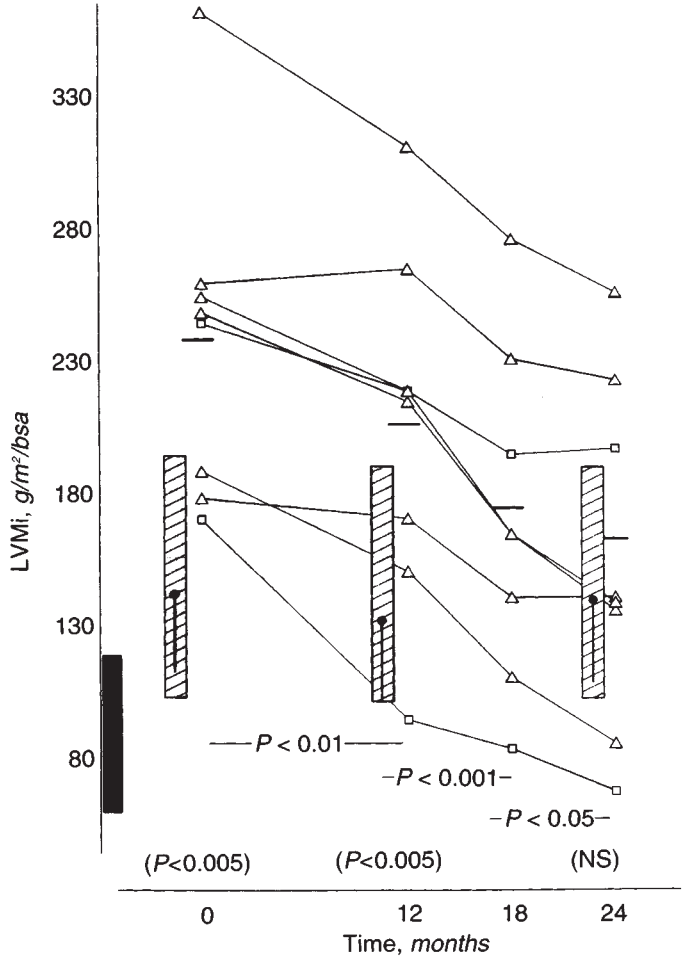

Fig. 2. *Indices of left ventricular mass (LVMi) for eight (2 females, □; 6 males, Δ) hemodialyzed hypertensive uremic patients before and after starting antihypertensive treatment with beta blockers, Ca antagonists and ACE inhibitors for 24 months.* Horizontal bars depict mean values. Also indicated are means ± SD and ranges (dashed columns) for nine sex- and age-matched normotensive dialyzed subjects. The shaded area on the vertical axis is the range for LVMi in 32 normal subjects. The *P* values for the between-groups differences (Student *t*-test for unpaired data, within parentheses) or within-groups (Student *t*-test for paired data) are shown.

Results

Table 1 shows some pertinent clinical data for both groups.

The average basal values for body wt, interdialysis body wt gain (Δ% body wt), kT/V, PTH, alkaline phosphatase and plasma aluminum concentrations of the two groups were very similar and did not change significantly during the study. Circulating Hb concentrations were also similar and increased significantly, although to a small extent, only in the HDH group.

Diastolic and systolic BP of the HDH patients decreased significantly ($F = 4.5$; $P = 0.0003$; $F = 6.3$; $P = 0.0001$; ANOVA) on antihypertensive therapy (Fig. 1). Two main drops were observed, the first between the first and the third months and the second between the 12th and the 15th months. After this time no further significant changes were seen. By definition, both the SBP and the DBP were significantly higher in the HDH than in HDN group. After the 12th month, however, the BP of both groups were no longer distinguishable. (Fig. 1).

At the end of the study period, when the CABPM collected for both groups were pooled and compared with the automated arm-cuff measurements, the differences were 2 ± 2 mm Hg for SBP and −1 ± 2 for DBP.

Table 2 lists data for echocardiographic records taken every twelve months for both groups of subjects.

Resting values for EDD, IVS and PW were all significantly higher in HDH than in HDN patients. On antihypertensive treatment, both EDD and the IVS decreased significantly to values that, after 24 months, were no longer significantly different from those of normotensive patients. The IVS/PW ratio for the HDH patients was higher than for the HDN group and decreased considerably thereafter, although still remaining higher than in the HDN group.

The baseline LVMi for the hypertensive patients was 239 ± 61 g/m^2, which was significantly greater ($P < 0.005$) than that of the normotensive patients (Fig. 2). During antihypertensive therapy there were significant decreases in the LVMi ($F = 40$; $P = 0.001$; ANOVA). Analysis of the individual basal data revealed that all patients from the HDH group had LVMi above the cut-off limit already established from normal subjects. It was also observed that three of eight hypertensive subjects had LVMi overlapping with those of the HDN group. After twelve months of treatment, the LVMi of the HDH group had decreased to 204 ± 67 g/m^2, which was significantly less than the baseline value ($P < 0.01$), but still greater than that for the HDN ($P < 0.02$). When the HDH were studied six months later, LVMi was found to have decreased further to a value of 173 ± 63 g/m^2, which is lower ($P < 0.01$) than that at the 12th month. When all the patients were restudied again at 24 months, the LVMi of the HDH patients had decreased to 161 ± 65 g, which was significantly lower ($P < 0.05$) than that at the preceeding

time and no longer significantly higher than that of the HDN group. At this time, three of eight hypertensive patients now had values for LVMi within, or even below, the range of LVMi for HDN subjects (Fig. 2).

Discussion

Severe LVH frequently develops in patients with end-stage renal disease [13] and is often associated with a poor cardiovascular prognosis [3].

Prospective echocardiographic studies have demonstrated the progressive nature of the disease, with both the thickness [5] and the internal dimensions [5, 6, 14] of the left ventricle tending to increase with time. Therefore, slowing the rate of this progression or reversing an already established LVH might be of major clinical importance for these patients with very poor cardiovascular prognosis. The pathogenesis of LVH in chronic uremic patients is a very complex problem involving many etiopathogenetic factors [14], with chronic anemia [4, 15, 16] and uncontrolled arterial hypertension [3, 4] possibly the main ones. However, while partial correction of the anemia by recombinant human erythropoietin (rHuEPO) has been shown to be effective in reversing the LVH in these subjects [16], the true effectiveness of antihypertensive therapy remained to be established [5, 17]. Since prospective studies specifically addressing this issue had never been done, we decided to do an echocardiographic study of the LV of a group of hypertensive dialyzed uremics, before and during long-term combined antihypertensive treatment. Since the purpose of this study was to elucidate the impact of the arterial hypertension on the LVM and the effects of the antihypertensive treatment on the natural course of LVH, patients were selected from a large population of hemodialysis patients to strictly avoid factors known to affect the LVM that might interfere with interpretation of the data.

In this work we set our target blood pressure arbitrarily at 150/90 and any BP above that level was defined as poorly controlled hypertension. Proper assessment of BP requires prolonged BP monitoring to ascertain the existence of an underlying arterial hypertension [18]. In the present study a whole-day ambulatory BP recording was made with a portable monitor and both the prevalence and the magnitude of the BP load were assessed on the basis of these repeated measures. After the start of the antihypertensive therapy, we monitored the BP by averaging three sets of measurements made after dialysis, on the following midweek interdialysis day, and just before the next hemodialysis. We were forced to use this method by the limited availability of portable monitors and the reluctance of the patients to undergo repeated troublesome whole-day BP recordings. However, we are confident that our schedule of monitoring the BP minimized the pitfalls intrinsic to the variability of scattered BP measurements. Indeed, when we measured the BP 24 months after the start of the study, there was good agreement between the BP collected by the arm-cuff device and that obtained with the portable monitor.

The antihypertensive regimen we used included beta-blockers, Ca antagonists and ACE inhibitors. Each of these drugs might have different and specific effects in lowering the LVM [19]. However, since it was beyond the scope of this study to ascertain by which mechanism the cardiac mass of hypertensive uremic patients was decreased, we gave a combination of these drugs in order to maximize their co-operative effects in both lowering the BP and reducing the LVH. The data presented here demonstrate that prolonged treatment with this type of combined antihypertensive therapy was able to considerably decrease the BP of already hypertensive hemodialyzed patients and to maintain a fairly constant BP level once the BP had become nearly normal.

In the last few years many factors have been suspected to be etiopathogenetic factors for LVH in chronic uremic patients, including uremic toxins, high PTH levels [14, 20] and aluminum overload [21]. The patients in this study were dialyzed according to widely accepted criteria for obtaining adequate dialysis. Their plasma aluminum levels were normal and did not vary throughout the study period, nor did their PTH levels.

Experimental studies have demonstrated that arterial pressure overload induces an increase in the end diastolic pressure which causes the LV to dilate until a concentric thickening of the wall supervenes, which then renormalizes the already increased wall stress and brings the left ventricular internal diameter back to the resting level [22]. In the present study, our hypertensive patients had dilated left ventricles with increased septal thickness and nearly normal PW. This picture, which is the pattern of asymmetrical septal hypertrophy [23], has already been reported for hemodialyzed uremic patients in previously published studies [5, 14, 15, 24]. Thus one might hypothesize that for some unknown reason, the PW of the LV of the uremic heart is unable to become adequately hypertrophic in response to the blood pressure overload, resulting in isolated septal hypertrophy and a widened internal LV chamber. In dialyzed uremics, however, the extent of LV dilation might also depend on the relative intravascular volume loading [25]. In our hypertensive patients, reduction of the blood pressure caused the EDD to decrease by about 20% and the IVS by about 13%. Thus, one might think that in these patients the calculated LVM was mainly decreased through some reduction of the intravascular volume load that both lowered the BP and reduced the EDD. To have an indirect estimate of the intravascular volume loading [7], we measured the interdialytic weight gains of both groups of patients. Pre-treatment values for Δ% body wt of the HDH subjects were similar to those of the HDN group and did not change thereafter, nor did their absolute body wt. Therefore, although we neither directly measured the blood volume nor determined their lean body mass, we believe it is unlikely that any major changes of the volume status of our patients might have taken place during the study period.

The data reported here contrast with previous reports on larger groups of dialyzed uremics, in whom progressive increases in either the EDD or the IVS were seen in spite of reported adequate control of the blood pressure [5, 6]. These reports, however, dealt with studies which were started before rHuEPO treatment was available.

Our subjects were treated with rHuEPO and care was taken to keep the Hb levels very close to a concentration of 10 g/dl. This might explain the differences from the studies above, which dealt with subjects in whom the underlying anemia might theoretically have offset the cardiac effects of the antihypertensive therapy. In another study, oral nitrendipine was given to a group of hemodialyzed hypertensives over a period of 24 weeks, and although it decreased the pre-dialysis BP, it did not

have measurable effects on heart size [7]. In our study, the antihypertensive therapy included three drugs and was prolonged for two years. Thus, it is possible that differences in selection criteria, in the mode of assessing the extent of the blood pressure load, in the antihypertensive drugs used, and in the length of treatment might all collectively account for the discrepancies between our findings and those reported by other groups. Analysis of the individual data revealed that the LVM of the hypertensive subjects overlapped with those of the normotensive patients, although their blood pressures did not. Furthermore, a supranormal average value for LVM in the HDN group also explained this partial overlap. These observations might raise the question as to the extent to which the high blood pressure is really important in inducing LVH in chronic uremic patients. In the past there has been considerable controversy as to whether the left ventricular hypertrophy of uremics is specific to them [26]. In experimental rats there was an increase in cardiac mass after subtotal nephrectomy, although the onset of arterial hypertension had been prevented by antihypertensive drugs and the anemia avoided by blood transfusions [27]. Furthermore, uremic patients are said to have a particular pathologic form of LVH in which intermyocardiocytic fibrosis is much more pronounced than in non-uremic hypertensive patients [28]. Thus we cannot exclude that there are some factors in patients with chronic uremia unique to the uremic status which might stimulate some growth of the interstitial ventricular myocardium independently of other causes known to induce the LVH.

Average values of LVM after 24 months of antihypertensive therapy were about 34% less than the pre-treatment values. Furthermore, analysis of the individual data demonstrated that the LVM of all the patients had decreased, with the final values for some of them lying below the upper limit of normal levels for healthy subjects. Thus, this study is the first to demonstrate that prolonged antihypertensive therapy with strict blood pressure control can consistently decrease or renormalize the size of the LV of chronically hemodialyzed uremic patients with LVM already increased.

Caution, however, must be used in extrapolating the conclusions drawn from our findings to the uremic population at large. In other poorly selected patients with more severe cardiac involvement, for example, calcific or ischemic cardiomyopathy, the likelihood of inducing regression of the LVH with strict blood pressure control would be poorer than for the small selected group of patients enrolled in this study.

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